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(71)Applicant : **NIPPON TENGANYAKU KENKYUSHO:KK**
(72)Inventor : **SHIBAZAKI YASUHEI**
YAMAKAWA YUKARI

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(54) TRANILAST PLASTER COMPOSITION AND ITS PRODUCTION

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a tranilast plaster composition excellent in skin permeability of tranilast.
SOLUTION: This tranilast plaster composition comprises either one or a mixture of tranilast and its salt as an active ingredient. The active ingredient containing a solubilizing agent and water is included in a plaster base in an uniformly dissolved state.

* NOTICES *

CLAIMS

[Claim(s)]
[Claim 1]A tranilast plaster body constituent characterized by containing either or those mixtures of tranilast and its salt as an active ingredient, and coming to contain in a plaster body base after this active ingredient has dissolved uniformly.
[Claim 2]A tranilast plaster body constituent characterized by coming to contain in a plaster body base after an active ingredient which contains either or those mixtures of tranilast and its salt as an active ingredient, and contains a solubilizing agent and water has dissolved uniformly.
[Claim 3]The tranilast plaster body constituent according to claim 2 which said plaster body substrate is a plaster body substrate for the skins, and is one sort as which a solubilizing agent is chosen from a group of alcohol amine and amino acid, or two sorts or more.
[Claim 4]The tranilast plaster body constituent according to claim 3, wherein said alcohol amine is one sort chosen from a group of N-methyl glucamine, diisopropanolamine, monoethanolamine, diethanolamine, and triethanolamine, or two sorts or more.
[Claim 5]The tranilast plaster body constituent according to claim 3, wherein amino acid is arginine.
[Claim 6]The tranilast plaster body constituent according to claim 2, wherein said plaster body substrate is an ophthalmic ointment substrate and said solubilizing agent is one sort chosen from a group of alcohol amine, or two sorts or more.
[Claim 7]The tranilast plaster body constituent according to claim 6, wherein said alcohol amine is one sort chosen from a group of monoethanolamine, diethanolamine, and triethanolamine, or two sorts or more.
[Claim 8]A manufacturing method of a tranilast plaster body constituent adding a surface-active agent after dissolving either or those mixtures of tranilast and its salt in solution containing a solubilizing agent, and kneading with a hydrophobic radical agent.
[Claim 9]A manufacturing method of a tranilast plaster body constituent characterized by kneading with a hydrophilic radical agent after dissolving either or those mixtures of tranilast and its salt in solution containing a solubilizing agent.
[Claim 10]A manufacturing method of the tranilast plaster body constituent according to claim 8 or 9, wherein said hydrophobic base material and said hydrophilic base material are ophthalmic ointment substrates.
[Claim 11]A manufacturing method of the tranilast plaster body constituent according to claim 8 or 9, wherein said hydrophobic base material and said hydrophilic base material are plaster body substrates for the skins.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the plaster body constituent which makes tranilast an active principle. It can be considered more as the plaster body constituent stable where high-concentration tranilast is dissolved in details by improving a base, and the cutaneous-absorption nature of the active principle in pharmaceutical preparation is excellent, and it is related with few plaster body constituents of skin irritation and eye stimulativeness.
[0002]Here, a plaster body is a concept containing ointment and the plaster.
[0003]Although the skin is a concept which is "one layer or the multilayer organization which has covered the body surface of metazoa" (Daijirin second-edition SANSEIDO 1995-11-3), and also contains in a broad sense the cell which constitutes eyes, such as the retina and a cornea, Suppose that it distinguishes separately and the mode, effect, etc. about an eye are written in this Description.
[0004]the plaster body constituent of this invention -- the case of the plaster body for the skins -- allergic dermatitis (atopic dermatitis.) keloid and a hypertrophic scar, eczema, and a dermatitis group (keratodermia tylodes palmaris progressiva.), such as cutaneous sensitization It is effective in the therapy of an itch group, (a hives Mr. lichen, straw FIRUSU, and fixed hives being included), Pruritus Cutaneous, a bug bite, psoriasis, palmoplantar pustulosis, etc. including lichen simplex chronicus Vidal, solar dermatitis, and circumference [lips] dermatitis.
[0005]In the case of an ophthalmic ointment, it is applicable to an operation of ischemic retina disease treating agents, such as vegetative form diabetes mellitus accompanied by the symptomatic therapy of the inflammatory disease of an ocular allergic disease, an ocular surface, and an anterior eye segment, and the vascularization, and eyes. The cornea treating agent for preventing turbidity of promoting recovery of the cornea after the optical corneal abscission operation which specifically uses ultraviolet radiation laser, especially an excimer laser especially in an operation of eyes, and a cornea, It is effective in the recurrence prevention agent as a therapy after a pterygium operation, the glaucoma postoperative filtration bleb maintenance effect and the intraocular pressure downward effect, and the depressor effect over the secondary cataract after intraocular implant insertion.
[0006]Here, although explained as a plaster body constituent mainly taking the case of an ointment constituent, it is not restricted to this.
[0007]
[Background of the Invention]Although tranilast is used as a treating agent of an allergic disease, and keloid and a hypertrophic scar, all are orally administered drugs, such as a capsule, a tablet, dry-syrups, and subtle granules. Ophthalmic solutions are also developed as a treating agent of an ocular allergic disease.
[0008]On the other hand, since a part is directly medicated with external preparations, such as an ointment, for example compared with an oral agent, injections, etc., a systemic side effect does not happen easily. Since the rise of concentration of drug is restricted to an application site, it is efficient when treating. The curative effect over skin disease, such as atopic dermatitis, keloid, a hypertrophic scar, is accepted by internal use, and, as for tranilast, development of the ointment

as a local administration agent is desired. And as for the field of the invention, drugs, quasi drugs, and cosmetics are contained.
[0009]And as a prior printed publication about the ointment of tranilast, there is JP,H6-128153,A, for example.
[0010]Tranilast which is an active principle does not dissolve in a base the tranilast plaster body constituent manufactured with this manufacturing method, but the crystal of tranilast is scoured by the base as it is (it is not desirable on cutaneous-absorption performance.).
[0011]That is, since tranilast hardly melted into water, it was thought that it was difficult to manufacture the pharmaceutical preparation containing high-concentration tranilast. Although tranilast melts into alkali, a precipitate is formed promptly. For this reason, even if it melts in alkali and kneads with an ointment base, a deposit of a crystal takes place in a base. The skin serves as a barrier to the foreign foreign matter. As for the permeability of the skin, it is desirable to be contained in an ointment base with the gestalt dissolved rather than the crystal grain child.
[0012]Also when it contains tranilast as an ophthalmic ointment, it is desirable to be contained in an ointment substrate with the gestalt dissolved rather than the crystal grain child. If point ON of the active principle in ophthalmic ointments is carried out to the saccus conjunctivae, it moves to an interface with tear fluid gradually by wink movement, begins to melt into tear fluid, and is absorbed to the angle conjunctiva. Therefore, the direction included with the gestalt which the active principle dissolved can shift early more.
[0013]However, in the limitation which this invention persons get to know, the tranilast ointment preparation which included tranilast in the ointment base in the state where it dissolved uniformly is not marketed.
[0014]
[Means for Solving the Problem]In order to solve an aforementioned problem, this invention persons were the processes in which it tried hard wholeheartedly at development, by using a specific solubilizing agent, not less than 10% and at least not less than 20 more%, found out that tranilast existed in a base in a form dissolved in stability for a long period of time, and thought out to a tranilast plaster body constituent of the following composition.
[0015]A tranilast plaster body constituent of this invention contains either or those mixtures of tranilast and its salt as an active ingredient, and comes to contain them in a plaster body base, after this active ingredient has dissolved uniformly.
[0016]That is, an active ingredient which contains either or those mixtures of tranilast and its salt as an active ingredient, and contains a solubilizing agent and water comes to contain a tranilast plaster body constituent of this invention in a plaster body base in the state where it dissolved uniformly.
[0017]In the above-mentioned composition, when using a plaster body substrate as a plaster body substrate for the skins, a solubilizing agent is made into one sort chosen from a group of alcohol amine and amino acid, or two sorts or more.
[0018]It is desirable to consider it as one sort chosen from N-methyl glucamine, diisopropanolamine, monoethanolamine, diethanolamine, and triethanolamine or two sorts or more as alcohol amine.
[0019]It is desirable to consider it as arginine as amino acid.
[0020]On the other hand, in the above-mentioned composition, when using a plaster body substrate as an ophthalmic ointment substrate, a solubilizing agent is made into one sort chosen from a group of alcohol amine, or two sorts or more.
[0021]It is desirable to consider it as one sort chosen from monoethanolamine, diethanolamine, and triethanolamine or two sorts or more as alcohol amine.
[0022]After manufacture of a tranilast plaster body constituent of this invention dissolves either or those mixtures of tranilast and its salt in solution containing a solubilizing agent, if it is necessary, it will add a surface-active agent, and manufactures it by kneading with a hydrophobic radical agent or a hydrophilic radical agent.
[0023]
[Detailed Description of the Means for Solving the Problem]The composition of this invention is

explained still in detail. Especially"%" that shows loadings by the following explanation, unless it refuses, "% of the weight" is meant.

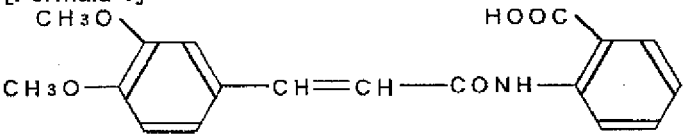
[0024]Artificers were able to complete the tranilast plaster body constituent in which skin permeability was extremely excellent, as a result of repeating examination wholeheartedly that the pharmaceutical preparation which is stability over a long period of time should be completed in the form which tranilast dissolved into the ointment base (plaster body base). Few ophthalmic ointments of eye stimulativeness were able to be completed. In order to carry out the high concentration dissolution of the tranilast which originally hardly dissolves in water, a specific solubilizing agent is used. It can manufacture regardless of a hydrophobic base and the base of hydrophilic nature by using these.

[0025]The tranilast used as an active ingredient of the plaster body constituent of this invention can also use a free object, salts, or those mixing. Although content can be suitably chosen according to the disease to apply, generally the high concentration is more desirable. At this invention, in the plaster body for the skins, although it is possible in 0.1 to 20% of range, it is 1 to 15% preferably. With an ophthalmic ointment, it is preferably usable in 0.3 to 3.0% of range 0.1 to 5.0%.

[0026]The tranilast used as an active ingredient by this invention is N-(3,4-dimethoxycinnamoyl) anthranilic acid expressed with a following formula.

[0027]

[Formula 1]



[0028]In a plaster body constituent of this invention, one sort chosen from a group of alcohol amine and amino acid or two sorts or more can be used with a plaster body constituent for the skins as a solubilizing agent.

[0029]As alcohol amine, N-methyl glucamine (meglumine, chemical name:1-methylamino 1-deoxy D-glycitol), It is desirable to use one sort chosen from a group of diisopropanolamine, monoethanolamine, diethanolamine, and triethanolamine or two sorts or more.

[0030]As amino acid, it is desirable to use arginine.

[0031]As a solubilizing agent in an ophthalmic ointment, one sort chosen from a group of alcohol amine or two sorts or more can be used.

[0032]It is desirable to use one sort chosen from a group of monoethanolamine, diethanolamine, and triethanolamine or two sorts or more as alcohol amine.

[0033]Tranilast is dissolved in solubilizing agent solution. In a plaster body for the skins, when a solubilizing agent was meglumine, not less than 25% of water content was required for a rate over the whole plaster body of solubilizing agent solution at this time to entire volume also at a hydrophobic radical agent or a hydrophilic radical agent. A crystal of tranilast deposited at 20% or less. When a solubilizing agent was diisopropanolamine, water content in which a hydrophobic radical agent or a hydrophilic radical agent also exceeds 20% to plaster body entire volume was required. A crystal of tranilast deposited in 15% or less of water content.

[0034]On the other hand, in an ophthalmic ointment, an initial complement of tranilast comes out in small quantities, and, for a certain reason, water content's [required for a relative target] becomes less than a case of a plaster body for the skins. For example, when a solubilizing agent was monoethanolamine and not less than 10% of water content was [solubilizing agents] diethanolamine and triethanolamine to entire volume, not less than 5% of water content was required to entire volume.

[0035]As for a maximum, it is more desirable to consider it as 70% or less of water content from a relation of viscosity in the range of a fat agent, although a hydrophobic radical agent and a hydrophilic radical agent are free.

[0036]Optimum concentration of a solubilizing agent in a solubilizing agent solution changes with

content of tranilast which he wishes eventually. That is, tranilast has the character to reduce pH, when it dissolves in an alkali solution. For this reason, in order to make the last pH into neutral vicinity (usually pH 6.5-8.0) from a standpoint of eye stimulativeness in pharmaceutical preparation, each quantity of a solubilizing agent and tranilast is decided uniquely.
[0037]In a plaster body for the skins, while tranilast shows solubility in following each meglumine diisopropanolamine concentration (entire volume standard) in the case of a 10% of content tranilast plaster body constituent, this invention persons are checking that each pH is shown.
[0038]In the case of 7.4; 7% of pH, meglumine 6% of case was case pHof 8.5; 8% of pH 9.2. In the case of 6.0; 4.2% of pH, diisopropanolamine 4% of case was case pHof 7.3; 5% of pH 8.4.
[0039]In an ophthalmic ointment, in the case of a 2.5% of content tranilast plaster body constituent. In view of a soluble standpoint, this invention persons are checking that the above is required triethanolamine 2.7% (pH 7.96) diethanolamine 0.93% (pH 7.94) to entire volume monoethanolamine 0.5% (pH 7.85) on an entire volume standard.
[0040]It turns out that what is necessary is just to change quantity of a solubilizing agent from the above thing in accordance with content of tranilast to wish so that pH of the last pharmaceutical preparation may become neutral vicinity with least skin irritation and eye stimulativeness.
[0041]Liquid in which solubilizing agent solution was made to dissolve tranilast serves as a uniform plaster body constituent by kneading as it is in the case of hydrophilic ointment.
[0042]However, in the case of a hydrophobic radical agent, the way things stand, in order not to be mixed uniformly, a nonionic surfactant is used. Generally a thing of 4-6 is suitably used for HLB as an emulsifier of a water-in-oil type (W/O). As a typical example, there are monostearin acid sorbitan;Span60 (HLB4.7) and monooleic acid sorbitan;Span80 (HLB4.3). 2 to 3% of entire volume is enough as the amount used.
[0043]As a base of an ointment for the skins, a hydrophobic radical agent or a hydrophilic base material of the following illustration can be used.
[0044]Hydrophobic radical agent : Vaseline, paraffin, Plastibase, silicone, Hydrophilic-radical agents, such as lard, waxes, unguentum simplex, and lead plaster: Hydrophilic ointment, hydrophilic petrolatum, purified lanolin, the Aqua hall, OISERIN, neo serine, absorption ointment, hydrous lanolin, hydrophilic Plastibase, macrogols, SORUBESU, etc.
[0045]Hydrophobic radical agent:vaseline, paraffin, Plastibase, hydrophilic radical agent:purified lanolin, etc. can be mentioned as a thing usable as an ophthalmic ointment substrate among the above.
[0046]A plaster body constituent of this invention may be used making it into ointment or plaster as it is on the occasion of actual use, and may be prepared in accordance with a conventional method to various dermal administration nature pharmaceutical preparation, such as attachment agents, such as a tape, or a hap agent.
[0047]In order to acquire the durability of an operation of an active principle, it is good also as a sustained release drug using a sustained-release base.
[0048]In manufacturing a plaster body constituent of this invention, an excipient used for preparation of the usual plaster body constituent can be used, choosing it suitably. For example, a surface-active agent, a stabilizing agent, an antiseptic, a moisturizer, and other additive agents can be made to contain suitably by request.
[0049]
[Example]Working example explains this invention concretely. This invention is not limited by working example.
[0050]A. The stability test was done about the pharmaceutical preparation for which the formation of stability test pharmaceutical preparation of pharmaceutical preparation was possible.
[0051](1) The following raw material was used for preparation of the testing-of-raw-material pharmaceutical preparation used for material and preparing method 1 test pharmaceutical preparation.
[0052]
Tranilast :. The OHARA Chemical Industries, Ltd. make meglumine :. Product diisopropanolamine made by SIGMA :. Wako monoethanolamine :. Wako diethanolamine :. Wako triethanolamine: --

Wako "Sepang 80":Katayama chemicals company make monooleic acid sorbitan white vaseline: -- hydrophilic ointment by MARUISHI Pharmaceutical Co., Ltd.: -- according to each formula shown in the preparing method <working example 1-7 and comparative examples 3-5> table 1 of 2 plaster-body constituent by MARUISHI Pharmaceutical Co., Ltd., and Table 2, Water was made to solubilize each solubilizing agent, tranilast was added further, after warming gently and making it dissolve at 60-70 **, this was added to the ointment base (in the canal formula, the nonionic surface active agent was added further), it often kneaded, and each tranilast ointment preparation for - eyes for the skins was prepared.

[0053]following the formula shown in the <comparative example 1 and 2> table 1 -- tranilast -- $NaHCO_3$ solution -- warming -- adding this to an ointment base, after making it dissolve (in a canal formula) furthermore, the nonionic surface active agent was added -- it often kneaded and tranilast ointment preparation was prepared 10% (it corresponds to working example 1 and 3 in JP,H6-128153,A).

[0054](2) Preservation condition above-mentioned each ointment preparation was saved by ** high temperature atmosphere and ** low temperature atmosphere of the following condition, respectively.

[0055]** Temperature conditions : 40 ** (**1 **), 75%RH (**5%)
use device: -- ADVANTEC low-temperature thermo-hygrostat AGX-326** temperature-conditions: -- 10 ** (**1 **)
Use device: The following item was examined for each ointment preparation saved on 311DSANYO medicinal refrigeration showcase MPR-3 test item and the test-method above-mentioned conditions about a total of five times after 1-2-3-4 weeks of preservation at the time of a start.

[0056]** Description examination : observe the color tone of a color, etc. visually.

[0057]** Survival-rate examination : measure precisely [water-repellent ointment pharmaceutical preparation] each ointment preparation 0.5g, add hexane 20mL correctly and shake it violently. This liquid is centrifuged (4000 rpm, 30min), and supernatant liquor is removed. Dissolving this sediment in dehydrated ethanol, it is referred to as 100mL (Table 2 50mL), and is considered as a sample undiluted solution. Sample undiluted solution 10mL is measured precisely, and internal standard solution 10mL (Table 2 5mL) is added correctly, and also dehydrated ethanol is added, and it is referred to as 50mL, and is considered as the sample solution. A tranilast reference standard is dried independently (105 **, 3 hours), and about 0.05 g of it is weighed precisely, and dehydrated ethanol is added, and it melts, and is correctly referred to as 100mL. This liquid 10mL (Table 2 5mL) is measured precisely, and internal standard liquid 10mL (Table 2 5mL) is added correctly, and also dehydrated ethanol is added, and it is referred to as 50mL, and is considered as a standard solution.

[0058]The 2000 time dehydrated ethanol solution of p-nitrobenzoic acid ethyl was used for the internal standard solution.

[0059]About sample-solution and standard solution 5muL (Table 2 10microL), it examined by liquid chromatography by the following operating condition, and asked for ratio Q_T of the peak area of tranilast and Q_S to the peak area of an internal standard substance, and the tranilast survival rate was searched for with the following formula.

[0060]survival-rate (%) $=Q_T/Q_{S\ --\ (g)}$ / [x reference standard output] 0.05x 0.5 / ointment output x100 chromatography operating condition: -- mobile phase: -- thinned glacial acetic acid (1->100) and acetonitrile mixture (3:2)
Detector: Ultraviolet absorptiometer (measured wavelength: 255 nm)
Flow: Adjust so that the retention time of tranilast may become about 7 minutes.

[0061]Column: Fill up a stainless steel tube about 4 mm in inside diameter, and about 15 cm in length with 5-micrometer octadecyl silanizing silica gel for liquid chromatographs.

[0062]column temperature: -- 30 ** sensitivity: -- 0.1AUFS sample preparation: -- direct sunlight is avoided and it carries out using the container which shaded.

[0063]Use device: Weigh precisely 0.5 g of Shimazu liquid chromatograph LC-A [10] [hydrophilic ointment preparation] this article, add correctly hexane 20mL and water 20mL, and shake them

violently. This liquid is centrifuged (3000 rpm, 10min), and the upper layer is removed, and let a lower layer be an extract. This extract 2mL is measured precisely, and internal standard solution 10mL is added correctly, and also dehydrated ethanol is added, and it is referred to as 50mL, and is considered as the sample solution. The following operation methods and how to ask are the same as that of water-repellent ointment pharmaceutical preparation.

[0064](3) The test result about each of a stability test result, an evaluation description examination, and a survival rate (40 **, 10 **) is shown in Tables 3, 4, 5, 6, and 7, respectively.

[0065]Tranilast is made to solubilize with each solubilizing agent, and it turns out that stability equivalent to a comparative example is shown as a petrolatum base and a hydrophilic ointment base, and the kneaded pharmaceutical preparation were shown in Tables 5, 6, and 7 under 40 **, 75%RH, and 10 ** preservation conditions.

[0066]B. About each ointment preparation for the skins (Table 1) prepared like the case of a stability test by the skin permeability test above, it carried out by the following method.

[0067]1) The radiographic examination method : the artificial skin (Alloask) was fixed to the Francis type diffusion cell, temperature was kept at 37 **, and the in vitro (inch vitro) penetration experiment was conducted under the protection-from-light condition. The 20 cm^3 effective diffusion surface area of the cell volume by the side of a receiver was 3.8cm^2.

[0068]The physiological saline was filled to the receiver side of a cell, and the skin was installed so that the dermis side of the skin might touch a physiological saline. 100 mg of pharmaceutical preparation was applied to the horny layer side, and this time was made into time zero. Under [a fixed quantity / amount / of tranilast / in a physiological saline / HPLC / it carries out 1mL sampling from the receiver side for every (at a total of five times 2**4**6**8**24 hours after) fixed time and]. Physiological saline 1mL which does not newly contain a drug was added to the receiver side of a cell after the sampling. The penetrable experiment calculated the average value repeatedly 3 times respectively altogether.

[0069]2) A test result and an evaluation test result are shown in drawing 1 and [Table 6 and] 2.

[0070]the accumulation skin transmission quantity of tranilast from the pharmaceutical preparation of the comparative examples 1 and 2 increased almost linearly with time, and the tranilast skin transmission rate from the pharmaceutical preparation of working example 1, 2, 3, and 4 was large from the first stage to a transmission rate being about 1 law in each time. Also in which time, there was much tranilast skin transmission quantity from the pharmaceutical preparation of working example 1, 2, 3, and 4 compared with the pharmaceutical preparation of the comparative examples 1 and 2. It is presumed to the pharmaceutical preparation of each comparative example being suspended type pharmaceutical preparation as this cause that it is because the pharmaceutical preparation of each working example is dissolved type pharmaceutical preparation.

[0071]C. According to the eye primary-stimulus sex-test 1 test-method Draize method, into the saccus conjunctivae of the right eye of a rabbit, eyewash was applied once and the closed eye of 50 mg (Table 2) of the administration pharmaceutical preparation was carried out for about 1 second. It presupposed no taking a measure as contrast to the left eye.

[0072]2) In accordance with [pharmaceutical preparation / valuation method / all the / ophthalmic ointment] the judging standard (Table 8, Table 9) of Draize, Using the naked eye or the slit lamp, fluorescein was used in 48 or 72 hours, it inspected about the existence of the abnormalities in a cornea after [1, 24, and 48] instillation and in 72 hours after [1 and 24] anterior eye segment inspections (a cornea, a conjunctiva, the iris, etc.) and instillation, by considering a left eye as contrast, and eye membrane primary-stimulus nature was evaluated.

[0073]3) A test result and an evaluation test result are shown in Tables 10, 11, and 12.

[0074]In the meglumine formula (comparative example 3), the diisopropanolamine formula (comparative example 4), and the L-arginine formula (comparative example 5), corneal opacity, hyperaemia circumcornealis, and the rubor, edema and secrete of the conjunctiva were accepted 1 hour after instillation. 24 hours after instillation, 1/3 example recovered such condition in the meglumine formula (comparative example 3) and the diisopropanolamine formula (comparative example 4), and it recovered thoroughly in the L-arginine formula (comparative example 5).

[0075]In the meglumine formula of 2.5% tranilast ointment, a diisopropanolamine formula, and an L-

arginine formula, since an epithelium-anterius-corneae obstacle is also observed, these things show that an ophthalmic ointment is unsuitable at an exam prescription of drug.

[0076]On the other hand, although all have very slight stimulativeness in a monoethanolamine formula (working example 5), a diethanolamine formula (working example 6), and a triethanolamine formula (working example 7), since the epithelium-anterius-corneae obstacle was not accepted, it turns out that it is useful as an ophthalmic ointment.

[0077]

[Function and Effect of the Invention]The tranilast plaster body constituent concerning this invention contains either or those mixtures of tranilast and its salt as an active ingredient, and since it is in the state which this active ingredient dissolved uniformly, the skin permeability of tranilast (active ingredient) is excellent as compared with the conventional example (comparative example). Eye stimulativeness falls as compared with a conventional example, and the ophthalmic ointment constituent concerning this invention has a more remarkable effect.

[0078]

[Table 1]

１０％トラニラスト皮膚用膏体処方 (単位：ｗｔ％)

	比較例１	比較例２	実施例１	実施例２	実施例３	実施例４
	疎水処方	親水処方	疎水処方		親水処方	
＜活性成分＞						
トラニラスト	10	10	10	10	10	10
＜塩基性水溶液＞						
1%NaHCO$_3$ aq	40	40	—	—	—	—
＜溶解補助剤＞						
メグルミン			6		6	
ジイソプロパノールアミン				4.2		4.2
＜H$_2$O＞	—	—	30	30	25	25
＜界面活性剤＞						
スパン８０	1.6	—	3	3	—	—
＜膏体基剤＞						
白色ワセリン	48.4		51	52.8	—	—
親水軟膏		50	—	—	59	60.8
ｐＨ	—	6.56	—	—	7.38	7.22

[0079]

[Table 2]

２．５％トラニラスト眼用軟膏処方（疎水処方） (単位：ｗｔ％)

	実施例５	実施例６	実施例７	比較例３	比較例４	比較例５
＜活性成分＞						
トラニラスト	2.5	2.5	2.5	2.5	2.5	2.5
＜溶解補助剤＞						
モノエタノールアミン	0.53					
ジエタノールアミン		0.95				
トリエタノールアミン			3.0			
メグルミン				1.64		
ジイソプロパノールアミン					1.2	
Ｌ－アルギニン						1.79
＜H$_2$O＞	25.0	25.0	25.0	25.0	25.0	25.0
＜界面活性剤＞						
スパン８０	1.0	1.0	1.0	1.0	1.0	1.0
＜膏体基剤＞						
白色ワセリン	70.97	70.55	68.5	69.86	70.3	69.71

[0080]

[Table 3]

	比－1	実－1	実－2	比－2	実－3	実－4
開始時	黄白色	微黄色	微黄色	黄白色	白色	白色
1週間後	黄白色	微黄色	微黄色	黄白色	白色	白色
2週間後	黄白色	微黄色	微黄色	黄白色	白色	白色
3週間後	黄白色	微黄色	微黄色	黄白色	白色	白色
4週間後	黄白色	微黄色	微黄色	黄白色	白色	白色

[0081]
[Table 4]

	実－5	実－6	実－7	実－5	実－6	実－7
	40℃、75%RH			10℃		
開始時	白色	白色	白色	白色	白色	白色
1週間後	白色	白色	白色	白色	白色	白色
2週間後	白色	白色	白色	白色	白色	白色
3週間後	白色	白色	白色	白色	白色	白色
4週間後	白色	白色	白色	白色	白色	白色

[0082]
[Table 5]
残存率（%）の結果（40℃、75%RH条件下）

	比－1	実－1	実－2	比－2	実－3	実－4
開始時	100	100	100	100	100	100
1週間後	99.4	99.1	100.1	105.4	97.9	99.5
2週間後	98.3	99.8	99.6	107.2	97.8	99.6
3週間後	99.7	99.1	99.8	108.2	99.9	100.6
4週間後	99.4	97.4	101.6	107.4	99.0	100.3

[0083]
[Table 6]
残存率（%）の結果（10℃条件下）

	比－1	実－1	実－2	比－2	実－3	実－4
開始時	100	100	100	100	100	100
1週間後	101.0	98.9	98.3	98.3	98.9	100.7
2週間後	102.9	97.0	99.4	97.5	98.9	99.8
3週間後	102.6	97.2	99.8	102.6	98.3	99.8
4週間後	103.2	99.4	99.1	108.8	97.9	100.6

[0084]
[Table 7]

残存率（%）の結果

	実－５	実－６	実－７	実－５	実－６	実－７
	４０℃、７５%ＲＨ			１０℃		
開 始 時	100	100	100	100	100	100
１週間後	101.1	99.6	99.9	99.4	100.4	100.1
２週間後	99.5	99.4	99.9	100.3	99.1	100.0
３週間後	98.1	99.5	100.2	99.3	99.9	99.5
４週間後	98.3	99.8	99.2	98.2	100.3	98.6

[0085]
[Table 8]

Draize法の眼反応の評価基準と評価（Draize、1959）

［Ｉ］角膜		
（Ａ）混濁の程度（最も濃い領域を判定する）		評点
透明：混濁なし		：０
散在性及び慢性の混濁、虹彩ははっきり認める		：１
半透明で容易に識別可能、虹彩はやや不明瞭		：２
乳濁、虹彩紋理認めず、瞳孔の大きさをやっと認める		：３
白濁、虹彩は認めない		：４
（Ｂ）角膜混濁部の面積		
０～１／４		：１
１／４～１／２		：２
１／２～３／４		：３
３／４～４／４		：４
（Ａ）×（Ｂ）×５	理論最大値	８０
［ＩＩ］虹彩		評点
（Ａ）正常		
正常以上のひだ、うっ血、腫脹、角膜周囲充血、（いずれか一つ、または組み合わせ）、多少とも対光反応あり		：１
対光反応なし、出欠、著しい組織破壊（いずれか一つ）		：２
（Ａ）×５	理論最大値	１０
［ＩＩＩ］結膜		評点
（Ａ）結膜の発赤（眼瞼結膜及び球結膜）		
血管は正常		：０
正常より明らかに血管は充血		：１
び慢性、深紅色で個々の血管は識別しにくい		：２
び慢性の朱肉様の赤色		：３
（Ｂ）結膜の浮腫		
腫脹なし		：０
正常よりいくぶん腫脹（瞬膜を含む）		：１
明らかな腫脹、眼瞼が少し外反		：２
腫脹、眼瞼が半分閉じる		：３
腫脹、眼瞼が半分以上閉じる		：４
（Ｃ）分泌物		
分泌物が認められない		：０
正常より少し多い		：１
分泌物があり、眼瞼とその近くの毛を濡らしている		：２
分泌物があり、眼瞼と毛のかなりの部分を濡らしている		：３
［（Ａ）＋（Ｂ）＋（Ｃ）］×２	理論最大値	２０

[0086]

[Table 9]

Kay and Calanda の眼粘膜刺激性の分類

点数	眼刺激評価
０．０～０．５点	刺激性なし
０．５～２．５点	ほとんど刺激なし
２．５～　１５点	ごくわずかな刺激性
１５～　２５点	軽度の刺激性
２５～　５０点	中等度の刺激性
５０～　８０点	高度の刺激性
８０～１００点	極度の刺激性
１００～１１０点	最極度の刺激性

[0087]
[Table 10]
薬剤処置眼におけるスコア集計結果

試験群	試験番号	1 hr			24hr			48hr			72hr		
		角膜	虹彩	結膜	角膜	虹彩	結膜	角膜	虹彩	結膜	角膜	虹彩	結膜
実−5	1	0	5	2	0	0	0	0	0	0	0	0	0
	2	0	5	2	0	0	0	0	0	0	0	0	0
	3	0	0	2	0	0	0	0	0	0	0	0	0
	合計	16			0			0			0		
実−6	1	5	0	2	0	0	0	0	0	2	0	0	0
	2	5	5	2	0	5	2	0	0	0	0	0	2
	3	0	5	2	0	0	0	0	5	0	0	0	0
	合計	26			7			7			2		
実−7	1	0	5	2	0	0	0	0	0	0	0	5	0
	2	5	5	4	0	0	2	0	0	0	0	0	0
	3	5	5	2	0	0	0	0	0	0	0	0	0
	合計	33			2			0			5		

[0088]
[Table 11]
薬剤処置眼におけるスコア集計結果

試験群	試験番号	1 hr			24hr			48hr			72hr		
		角膜	虹彩	結膜	角膜	虹彩	結膜	角膜	虹彩	結膜	角膜	虹彩	結膜
比−3	1	5	5	2	0	5	2	0	0	0	0	0	0
	2	5	5	10	5	5	2	0	0	0	0	5	0
	3	0	5	6	0	0	2	0	0	0	0	0	0
	合計	43			21			0			5		
比−4	1	5	5	8	5	5	2	0	0	0	0	0	0
	2	5	5	8	0	5	2	0	0	0	5	0	0
	3	5	5	8	0	0	0	0	0	0	0	0	0
	合計	54			19			0			5		
比−5	1	0	5	6	0	0	0	0	0	0	0	0	0
	2	5	5	6	0	0	0	0	0	0	0	0	0
	3	5	5	2	0	0	0	0	0	0	0	0	0
	合計	39			0			0			0		

[0089]
[Table 12]

眼粘膜一次刺激性の判定

試験群	動物数	総平均評点*				判定
		1hr	24hr	48hr	72hr	
実－５	３	５	０	０	０	ごくわずかな刺激性
実－６	３	９	２	２	１	ごくわずかな刺激性
実－７	３	１１	１	０	２	ごくわずかな刺激性
比－３	３	１４	７	０	２	ごくわずかな刺激性
比－４	３	１８	６	０	２	軽度の刺激性
比－５	３	１３	０	０	０	ごくわずかな刺激性

＊評点総計／動物数

[Translation done.]